IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: GERSHONI 5

In re Application of:	)	Conf. No.: 1117
Jonathan GERSHONI et al.	)	Art Unit: 1634
Appln. No.: 09/297,668	)	Examiner: Betty J. Forman
Filed: May 6, 1999	)	Washington, D.C.
For: DETERMINATION AND CONTROL OF BIMOLEECULAR INTER-ACTIONS	)	July 22, 2002

AMENDMENT

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action of February 21, 2002, petition for a 2-month extension of time and payment being attached hereto, please amend as follows:

In the Claims

Please amend claim 159 as indicated.

159 (Amended). A method of preparing a library of peptides which can be screened to find peptides which interact with ligands which interact with discontinuous epitopes of a single biological unit, comprising:

E1

(a) providing a plurality of DNA fragments, which fragments appear in a DNA sequence which encodes said single biological unit;

(b) creating a library of oligonucleotides, each said oligonucleotide comprising at least two of said fragments, said fragments being randomly ligated;

E1 cont.

(c) inserting each of said oligonucleotides into an expression system; and

(d) causing the peptides encoded by said oligonucleotides to be expressed, thereby preparing a library of peptides.

[Please insert new claims 177-182 as follows:]

177 (New). A method in accordance with claim 144, wherein each of said DNA fragments of (a) has a size of about 50 to about 150 base pairs.

E2

178 (New). A library of peptides in accordance with claim 158, wherein each of said peptide fragments has a size of about 17 to about 50 residues.

179 (New). A method in accordance with claim 159, wherein each of said DNA fragments of (a) has a size of about 50 to about 150 base pairs.

180 (New). A method in accordance with claim 171, wherein each of said DNA fragments of (a) has a size of about 50 to about 150 base pairs.

181 (New). A method in accordance with claim 175, wherein each of said DNA fragments of (a) has a size of about 50 to about 150 base pairs.

E2 cont.

182 (New). A library of oligonucleotides in accordance with claim 176, wherein each of said DNA fragments has a size of about 50 to about 150 base pairs.

REMARKS

Claims 144-182 presently appear in this case. Claims 157, 158, and 171-176 have been withdrawn from consideration. No claim has been allowed. The official action of February 21, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

The examiner has withdrawn the previous restriction requirement and issued a new requirement under 35 U.S.C. 121 and 372. The examiner states that the groups of inventions which are not so linked as to form a single general inventive concept include:

Group I - including claims 144-156 and 159-170, drawn to a method of identifying and producing a peptide;

Group II - including claim 157, drawn to a method of vaccinating;

Group III - including claim 158, drawn to a library of peptides;

Group IV - including claims 171-175, drawn to a method of identifying and producing an oligonucleotide; and

Group V - including claim 176, drawn to a library of oligonucleotides.

The examiner states that the technical feature linking Groups I-V appears to be that they all relate to a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit, wherein the peptide is produced by providing and randomly ligating a plurality of DNA fragments which encode the single biological unit. The examiner states, however, that Marks teach the peptide and method of making the peptide as claimed and therefore the technical feature linking the groups does not constitute a special technical feature as defined by PCT Rule 13.2. This restriction requirement is respectfully traversed.

In order to be responsive, applicant affirms the provisional election previously made with traverse to prosecute the invention of Group I, including claims 144-156, and 159-170. It is urged, however, that the special technical feature of the present invention is not disclosed by Marks, or any of the other references of record. The basic concept which is the special technical feature of the present invention relates to the creation of a library of oligonucleotides in which each oligonucleotide of the library comprises at least two fragments, randomly ligated, which fragments appear in a DNA sequence which encodes a single biological unit. In Marks, the single biological unit is a single antibody. The only fragments of a single antibody which are formed by Marks are a heavy chain fragment and a light chain (which is technically not a fragment, but an

entire chain). To the extent that a "plurality" can include two, it can be said that Marks provides a plurality of DNA fragments which encode a single biological unit, as Marks provides two, and only two such DNA fragments one V_H and one V_L. However, it cannot be said that Marks creates a library of oligonucleotides by randomly ligating those two fragments. Two fragments cannot be randomly ligated to form a library. Besides, for the reasons discussed below with respect to Huse, only one oligonucleotide is made in a typical construct used for the purposes of Marks. Thus, Marks does not teach the process of the present invention or any peptide which can be found thereby. Accordingly, Groups I-V are linked by the same or corresponding special technical feature so as to form a single general inventive concept. Reconsideration and withdrawal of this restriction requirement and examination of all the claims now present in the case, is therefore respectfully urged.

Claims 159-171 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite because the claim is drawn to a method of preparing a library of peptides, but the method does not recite a step of library preparation. The examiner suggests that claim 159 be amended, for example, to insert at the end "thereby preparing a library of peptides".

Claim 159 has now been amended in the manner suggested by the examiner, thus obviating this rejection.

Claims 144-146, 149-151, 155, 156, 159-161, 163-165, 169 and 170 have been rejected under 35 U.S.C. 102(b) as being anticipated by Huse. The examiner states that Huse discloses a method of identifying and producing a peptide which interacts with a ligand which interacts with a discontinuous epitope of a single biological unit by providing a plurality of DNA fragments which appear in a DNA sequence encoding the single biological unit (i.e., antibody); creating a library of oligonucleotides comprising at least two randomly ligated DNA fragments; inserting each of said oligonucleotides into an expression system; expressing the peptides encoded by the oligonucleotides; screening the expressed peptides for interaction with the ligand that interacts with the discontinuous epitope (i.e., antigen); identifying the peptide and producing the identified peptide. The examiner states that given the broadest reasonable interpretation of the claims, the claimed single biological unit encompasses the antibody of Huse, and therefore Huse discloses the method of these claims. This rejection is respectfully traversed.

The technology of Huse is totally different from that of the present invention and bears no similarity conceptually nor technically. Cloning consecutive DNA fragments is not new. The present invention is directed to the use of various methods to generate tandem peptides designed to simulate and satisfy discontinuous conformational surfaces of a given protein (i.e. tertiary conformations).

More specifically, the present invention seeks to functionally reconstitute the elements of a single protein's tertiary conformation. This is accomplished by juxtaposing linear peptides non-naturally, i.e., peptide fragments of a protein that are never in direct linear continuum (i.e., in the primary conformation), in the native protein.

In Huse, a phage expression system is used to produce Fab fragments. In principle, Huse does not create combinations to generate novel structures derived from a single polypeptide, and thus does not deal in any way with tertiary structures. Huse attempts to generate repertoires of novel quaternary structures. The whole methodology of Huse relies on maintaining the integrity of each polypeptide component and its primary conformation and merely mixing multitudes of heavy chains and light chains to create libraries of Fabs. This is like shuffling the various heavy chains and light chains so that different components can be mixed together. However, the natural position of the elements as found in the native proteins, is always ensured and never disrupted. In Huse, a diversity of light chains are allowed to form Fabs with a diversity of heavy chains, all the while maintaining the native primary, secondary, and tertiary conformations of each. In the present invention the method is based on generating novel primary structures to simulate functional tertiary surfaces.

The examiner states that the "single biological unit" of the present claims can be an antibody. Applicant agrees. However, a single biological unit is a single antibody, not the multitude of different antibodies found in a mouse spleen. In claim 144, paragraph (a) involves providing a plurality of DNA fragments, which fragments appear in a DNA sequence which encodes said single biological unit. The only "fragments" provided from a single antibody by Huse, is a V_H fragment which includes the entire variable region of the immunoglobulin heavy chain and a V_L fragment, which includes the entire light chain. Thus for any single biological unit, i.e., single antibody, only two fragments are produced. Technically two can be "a plurality", so the procedure of (a) may technically be met by the process of Huse. However, paragraph (b) is not. Paragraph (b) involves creating a "library of oligonucleotides", each said oligonucleotide comprising at least two of said fragments, said fragments being randomly ligated. The plurality of DNA fragments obtained in the procedure of (a) contains only two fragments. One cannot create a "library of oligonucleotides" from only two fragments being randomly ligated. While a claim must be given its broadest reasonable interpretation, a library cannot consist of only one member. Furthermore the library of Huse contains a lot more than ligated fragments from a single biological unit. It contains ligated fragments from an entire library of biological units.

It can be seen from Figure 1 of Huse, that the combinatorial construct always has the heavy chain fragment in one place and the light chain fragment in another place, downstream thereof. Thus, the only oligonucleotide that could be made by Huse which contains two DNA fragments from a single biological unit, is one in which the heavy chain fragment and the light chain fragment are both present in the single combinatorial construct as shown in Figure 1 of Huse. Huse does not even contemplate putting the fragments in a different order. They can only be in one order on the construct, with the heavy chain upstream of the light chain. Thus, it cannot be said that the fragments of Huse are randomly ligated. The two fragments from a single biological unit are ligated rationally in a single order. There is nothing random about it whatsoever. The single combinatorial construct with the two fragments from a single antibody is not a "library of oligonucleotides" by any definition of the term "library", and it cannot be said that in the single oligonucleotide of Huse which includes such fragments, such fragments are "randomly ligated". They are ligated in a very specific and definite manner, and not randomly. The only thing random in Huse is the selection of fragments from <u>different</u> biological units. There are no fragments of a single biological unit randomly ligated into a library of oligonucleotides.

Accordingly, as procedure (b) of claim 144 is not conducted by Huse, claim 144 is not anticipated by Huse and

none of the dependent claims from claim 144 can be anticipated by Huse. Claim 159 contains the same paragraphs (a) and (b) as in claim 144, and therefore claim 159 cannot be anticipated by Huse for the same reasons discussed above with respect to claim 144. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 147, 148, 154, 162, and 168 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Huse in view of Stemmer. The examiner states that Stemmer teaches mechanical cutting of DNA and that it would be obvious to modify the enzyme digestion of Huse with the mechanical shearing of Stemmer. The examiner also states that Stemmer teaches synthesis of DNA units and it would be obvious to do so in the process of Huse, and that Stemmer teaches a eukaryotic expression system which would be obvious to use in the process of Huse. This rejection is respectfully traversed.

Stemmer supplies none of the deficiencies of Huse as discussed hereinabove specifically with respect to procedure (b) of claims 144 and 159. Accordingly, no combination of Huse or Stemmmer arrives at or makes obvious the method of the present invention. Reconsideration and withdraw of this rejection is therefore also respectfully urged.

Claims 152, 153, 166 and 167, have been rejected under 35 U.S.C. 103(a) as being unpatentable over Huse in view of Marks. The examiner states that Marks teaches inserting

oligonucleotides into the coat proteins to display antibodies on phage, and that it would have been obvious to modify the phage in the method of Huse by inserting the oligonucleotide in the coat protein of filamentous phage as taught by Marks. This rejection is respectfully traversed.

Marks fulfills none of the deficiencies of Huse as discussed above with respect to claims 144 and 159. As the independent claims are novel and unobvious, then all of the claims dependent there from must be novel and unobvious for the same reasons. Reconsideration and withdrawal of this rejection is also respectfully urged.

New claims 177-182 have now been added which specify that each of the DNA fragments of (a) has a size of about 50 to about 150 base pairs. This is supported for example in the present specification at page 18, lines 24-25. The method of Huse deals with mixing entire light chains with heavy chain fragments to generate classical Fabs. These are at least hundreds of residues long and the final product is about 50 kDa. This is markedly and conceptually different than the present efforts to reconstitute a functional subdomain containing less than 100 amino acids derived from the intact protein. The Huse technology teaches how to reconstitute intact full size all-encompassing Fabs, where the method of the present inventions specifically shys away from the fullness and intactness of the protein. The intent is to simulate the functional limited surface of the protein using

isolated fragments of the protein and not entire subunits. Accordingly, new claims 177-182 further distinguish the present invention from any of the references of record, and they are patentable in their own right. Independent consideration of these claims is therefore also respectfully urged.

It is submitted that all the claims now present in he case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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